REMARKS

Claims 2-7, 10, 11, 16-20, 22-26, 29-35, 37 and 40-45 will remain in the application for further prosecution after entry of the proposed amendments. New Claim 45 has been added to replace canceled Claim 21, with Claims 22, 24, 25, 26, 29-31, 33, 35, 37 and 43 amended to correct their dependency. Claims 38 and 39 have also been canceled. Claims 23-26, 29, 30, 35 and 37 have been amended to further distinguish the present invention from the cited references, which are discussed below.

Rejections Under 35 U.S.C. 112

Claims 21-26, 29-35 and 37-43 have been rejected under the first paragraph of 35 U.S.C. 112 as failing to comply with the written description requirement. The Examiner contends that the specification does not support the term "predetermined **fixed** liquid volume". This rejection may have been rendered moot in view of the replacement of Claim 21 with Claim 45.

The Applicants' method requires that it is carried out within a device having defined physical parameters, which is inherently operated in a batch manner. Predetermined volumes of liquid contained in wells are transferred to chambers for mixing, the chambers being larger than the combined volume of the wells. The word "fixed" was intended to emphasize the term "predetermined liquid volume". It has been deleted in the above amendments.

When predetermined volumes are combined and mixed in subsequent chambers, the volume of chambers is defined with respect to the combined predetermined volumes of the wells supplying the chambers. For example, in Claims 25 and 26 the first and second chambers have volumes at least about twice that of the combined predetermined liquid volumes. In claims 29

and 30 at least 100 μm is provided above the combined liquid level. Given a predetermined volume of the wells, it is possible to determine the size and dimensions of the mixing chambers.

Applicants' microfluidic device inherently operates in a batch mode and the claims should not be construed to include continuous operation. No specific structure is needed to demonstrate that the Applicants' device inherently is operated in a batch manner. The device is intended to receive a predetermined amount of liquid sample and then process it to measure the amount of an analyte in the sample. Thus, the mixing of the sample with other liquids, i.e. reagents and the like, is intended to produce reactions with the sample that can be measured. Those measurements must be related to the fixed amount of the sample and consequently the device must operate in a batch manner. All of the figures and the examples support such an understanding. In Example 1 a fixed (predetermined) volume (10uL) of a liquid was added to sample well 10. Well 14 was filled with 10uL of another liquid. The two liquids were sent at the same time to first Chamber 18 having a volume of 36 μL, then to Chamber 22 having a capacity of 26 μL.

Furthermore, since the 1st and 2nd chambers have greater volumes than the combined volume of the wells receive the liquids to be mixed, space will remain in the 1st and 2nd chambers after they have received the mixed liquids. However, if liquids are added to the wells after they are filled, which is required by continuous operation, then the 1st and 2nd chambers will be filled and overflow. There will be no space for mixing of the liquids, which the claims require. Therefore, batch operation is inherent in both the method and the device claims and continuous operation is excluded.

Claims 25-28, 29-30, and 36 [sic] have been rejected as indefinite. Claims 27, 28 and 36 have previously been canceled. These are microfluidic device claims, that is, they define the volume of the first and second chambers (claims 25, 26, 29, 30) with relation to the volumes of the first and second liquid wells of Claim 45. The Examiner contends that the volumes are related to the operation of the device and cannot be determined. This issue raises again the question of batch operation discussed above. The size of the first and second chambers is related to the volume of the wells supplying them. The Examiner should understand that "volume" refers to structure, not just the amount of liquid being moved through the device when it is operated. The volume of a sample well defines both the dimensions of the well and how much liquid the well will hold. In a batch operation the entire volume of a well would be filled and then transferred to the first and second chambers. If less than the entire volume were to be transferred, which clearly would not be intended, the first and second chambers would still mix liquids, since they would have extra space beyond that provided according to claims 25, 26, 29 and 30.

Claim 21's replacement, Claim 45, has been written to avoid its being interpreted as involving the intended operation of the microfluidic device. While the Applicants disagree that Claim 21 should be read to involve the volume of liquids being mixed, as revised in Claim 45 the issue has been obviated.

Rejections Under 35 U.S.C. 103

Claims 2-4, 6, 7, 10, 11, 16, 18-26, 29-35, 38, 40 and 42-44 have been rejected under 35 U.S.C. 103(a) as unpatentable (i.e. obvious) over Kellogg, et al (US 6,063,589) ("Kellogg") in view of Koop, et al (US 6,457,854) ("Koop"). The Applicants believe that Koop's device

operates in a continuous mixing mode and is therefore not relevant to their microfluidic device, which inherently operates with predetermined liquid volumes, i.e. it is a batch operated device. The Examiner's response to the Applicant's argument makes it clear that, despite the description and examples, he continues to believe that the device could be operated continuously. Kellogg, however, clearly involves a batch operated device.

Kellogg uses centrifugal force to move the liquids to be mixed. In fig. 14-15, Kellogg measures two liquids in a series of capillaries 602 and then discharges them by centrifugal force, where they join and pass through a mixing chamber 605 (see Example 5, column 45). Kellogg states in column 46, lines 11-14 that "fluid flow within mixing chamber 605 was turbulent, in contrast to fluid flow through capillary barrier 603 or channel 604, which was primarily laminar, so that mixing occurred predominantly in mixing chamber 605." (emphasis supplied).

The mixing chamber 605 is clearly smaller than the volume of the combined liquids, as also is the receiving chamber 606. Therefore, Kellogg does not teach essential features of the Applicant's invention, which includes no mixing chamber and uses chambers of larger volume than the liquids being mixed. Fig. 14 is somewhat misleading. As described more definitely at column 45, the following sizes can be determined.

	Volume, μL	Dimensions
Metering array 602	25 μL each	0.5 x 0.5 x 16.6 x 6 = 25 $(mm)^3$ = 25 μL Col. 45, line 24
Mixing chamber 605	3 μL	0.75 x 2 x 2 = 3 $(mm)^3$ = 3 μL Col 45, lines 42-43
Receiving chamber 606	18.75 μL	5 x 5 x 0.75 = 18.75 $(mm)^3$ = 18.75 μL

		Col. 45, lines 62-63

The volumes of both the mixing chamber 605 and the receiving chamber were smaller than the volume of either of the metering arrays. These features were placed so that the centrifugal force on the liquids increased by the square of the instance from the center. The liquids were driven to greater speeds as they moved outwardly from the entry ports 601. It follows that this acceleration must have been involved in the mixing. Therefore, Kellogg teaches a mixing system that is clearly not the same as that of the Applicants. Furthermore, there is no evident reason why one skilled in the art would conclude from Kellogg that the Applicant's method and device would provide satisfactory mixing. The difference between the device of Kellogg and that of the Applicants is not merely a matter of modifying volumes and dimensions to optimize results. One skilled in the art would assume that Kellogg had already done that and arrived at a different design consistent with his centrifugally driven platform.

In order to fit Kellogg into the Applicant's claims, the Examiner is required to define the combination of 605, 610 and 606 of Fig 14 to be a first chamber. Kellogg calls 605 a "mixing chamber" and 610 is "a capillary passageway". Kellogg's description should be aligned with the applicant's claims such that 605 is the first chamber and 606 the second chamber. Then, it will be evident that Kellogg fails to make obvious the Applicant's device. Mixing chamber 605 is clearly much smaller than the combined volume of the capillaries 602. This is also true of the devices shown in Examples 6 and 7 (Fig. 17 and 23), where the mixing chambers (657 and 807) are very small. It seems likely that the Kellogg mixing chambers are intentionally made much smaller than the combined liquids in order to create turbulence that results in mixing. The larger

"mixed fluid receiving chamber" 606 receives the mixed fluids. It's large volume is not used to complete mixing.

Capillary 610 is not a chamber and since it connects 605 and 606, it must correspond to the connecting capillary (or capillaries) between the Applicant's first and second chambers. By combining 605, 610 and 606, the Examiner has not only ignored the clear intentions of Kellogg, but has made it necessary to reply on Koop as a secondary references.

Koop teaches a continuous mixing system which does not involve combining predetermined volumes of liquids by moving them into chambers which have volumes greater than that of the combined liquids. Therefore, Koop does not overcome the deficiency of Kellogg.

In his extended defense of the pertinence of Koop, the Examiner continues to ignore the difference between a device for mixing of two continuously flowing streams (Koop) and a device for mixing in a batch operation two predetermined volumes of liquids (e.g. Kellogg and the present device). Koop has no chambers corresponding to those of Kellogg and the Applicants. Instead, Koop merely causes two passages to intersect and then divide again. There is no "chamber" at the intersection and it would be impossible for the intersection to have a space larger than the combined liquids, since they are continuously flowing through the intersection.

Since Koop did not teach the mixing of predetermined volumes of liquid in a batch operation, the Examiner's reliance on case law related to "routine skill in the art" is misplaced. Koop cannot be adapted by "routine skill in the art" to add chambers in a batch operated device, which chambers are larger than the combined volumes of the liquids being mixed.

Claims 5, 17, 37, 39, and 41 have been rejected under 35 U.S.C. 103(a) as unpatentable over Kellogg in view of Koop and further in view of Jakajima et al [sic] (Nakajima). These claims depend from independent claims 44 and 45. They should be allowable if the Examiner argees with the Applicants that Claims 44 and 45 are patentable over Kellogg and Koop. The Examiner errs in stating that "Koop...described all of the recited subject matter within the scope of the claims with the exception of..." Koop does not teach the method of Claims 44 et al or the device of Claims 45 et al, as has been discussed above. Koop has no wells for holding and defining the amount of the liquids to be mixed, he has no chamber having a volume larger than the volume of the combined wells, and he has no ability to combine defined amounts of liquids in a chamber.

Nakajima describes an improved device to create emulsions from a dispersed phase containing particles and a continuous phase. The Nakajima device employs structures that are far different from those of the Applicants' device. The Examiner relies on "obvious to one skilled in the art" to combine Nakajima with Koop. However, combining Nakajima with Koop would not yield the Applicants' invention. Furthermore, neither Kellogg nor Koop nor the present invention involve forming emulsions. Rather, they mix two liquids to produce a homogenous mixture. Consequently, Nakajima is non-analogous art.

Nakajima is totally different from the Applicant's device and method and from Kellogg and Koop. Nakajima proposes an improvement of their previous device (shown in Figs. 10-13) in which, instead of mixing two liquids, one liquid (containing dispersed particles) is formed into microspheres within a second liquid (the continuous phase) to create an emulsion. Thus, the Nakajima device is clearly non-analogous art. Nakajima does not mix two liquids but suspends

microspheres of one phase in another phase. Any structures suitable for Nakajima's purpose would be irrelevant to the Applicant's purpose, or at least not what one skilled in the art would consider for use in the Applicant's device.

Comments on the Examiner's Response to Arguments

10. The Applicant's claims do not require limitations to exclude a continuous mode of operation. Such operation is inherent in the principal independent claims 44 and 45 as explained above. No control system or valves are required.

11. Replying on the extreme end of Kellogg's nominal range of 1-150μl is unreasonable. This could only apply to Example 5 of Kellogg. In Example 6 and 7, the mixing chambers (657 and 807) apparently contain less than 1μl. However, even in Example 5, calculation will show that dividing 1μl of a liquid evenly across the seven capillaries of 602, each of which can contain 3.6μl (25 μL/7) would be unlikely. Consequently, the low volume of 1μl suggested by Kellogg must relate to a smaller embodiment, which necessarily would have a much smaller mixing chamber than that of Example 5 (3μl) in order to achieve turbulence and mixing of the two liquids.

13. Citing case law is not a substitute for facts and reasons. The Applicant's contend that Koop cannot be combined with Kellogg to reach the Applicant's device. Koop not only discloses a different system for continuously mixing two liquids, but has intersections that are not chambers having volumes larger than the volumes of the liquids being mixed.

14. There is nothing in Nakajima that suggests the Applicant's invention. Furthermore, Nakajima is only applied against dependent claims which should be allowable if Claims 44 and 45 are patentable over Kellogg and Koop, as the Applicant's contend.

In view of the amendments and the above remarks, the claims are believed to be in condition for allowance. If further amendment is believed necessary, the Examiner is invited to contact the Applicants' attorney, at the telephone number provided below.

Respectfully submitted,

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